PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/001333	06.04.2005	08.04.2004

International Patent Classification (IPC) or both national classification and IPC
C07D403/14, C07D223/16, C07D401/12, C07D401/14, C07D413/14, C07D403/12, A61K31/55, A61P25/00

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/001333

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 7

because:

☒ the said international application, or the said claims Nos. 7 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2
	No:	Claims	1,3-9
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-6,8,9
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I
Basis of the opinion

The application is directed to
(i) tetrahydrobenzo[d]azepines (I) (claims 1-2),
(ii) a pharmaceutical composition with a compound (I) (claim 3),
(iii) the medical use of compounds (I) (claims 4-6),
(iv) the corresponding therapeutic method (claim 7),
(v) the medical use of the pharmaceutical composition (claim 8), and
(vi) a process for the preparation of compounds (I) (claim 9).

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 7 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item IV
Lack of unity of invention

See item V.3.3 below.

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: WO 2004/018432, 4 March 2004; cited in the application.
D2: WO 2004/026305, 1 April 2004; cited in the application.
D3: WO 2004/035544, 29 April 2004.
D4: WO 20047056369, 8 July 2004.

D5: WO 2005/014479, 17 February 2005.
D6: WO 2005/039591, 6 May 2005.

D3 to **D6** were published after the priority date. Under the presumption that the priority is valid for the claimed matter these documents are not considered as prior art under Rule 64.1 PCT.

2 Novelty

The application does not comply with the criterion of novelty for the following reasons.

2.1 **D1** discloses histamine H_3 receptor antagonists according to the present formula (I) wherein R^1 is C_{2-4}alkyl or -CH_2-C_{3-7}cycloalkyl and R^2 is -X-heterocyclyl with X being C_{2-5}alkylene and heterocyclyl being piperidin-1-yl and pyrrolidin-1-yl (cf. claims 1 and 8). The document, furthermore, discloses the preparation of these compounds according to present claim 9 (cf. e.g. page 13, scheme 1), a pharmaceutical composition comprising them (claim 9), and it teaches that these antagonists are useful in the treatment of diseases responsive to the inactivation of the histamine H_3 receptor (page 42, last paragraph). As the H_3 receptor is primarily expressed in the brain, notably in the thalamus and caudate nucleus (**D1**, page 42, last paragraph), it is concluded that these diseases represent neurological diseases. Hence, the subject-matter of the present claims 1 and 3-9 lack novelty for the whole overlapping range with document **D1**.

D2 discloses opioid receptor antagonists, their preparation, a pharmaceutical composition comprising them, and their medical use in the treatment of neurological disorders such obesity-related depression or anxiety, and stroke (cf. claim 30). The compounds of **D2** overlap with the present compounds (I) when R^1 is optionally substituted C_{2-7}alkyl or C_{3-7}cycloalkyl and R^2 is $CONR^5R^6$-substituted -X-aryl or -X-heteroaryl with X being a bond (cf. **D2**, claim 1, wherein ring A is a benzene ring; $(CR^3R^{3'})_v$ is -CH_2-CH_2-; R^2 is C_2alkyl attached to ring A to form a 7-membered nitrogen-containing bicyclic heterocycle; R^1 is C_{1-8}alkyl, C_{3-8}cycloalkyl, -C_{1-8}alkyl-C(O)-C_{1-8}alkyl, C_{1-8}alkoxy-C_{1-8}alkyl, -$(CH_2)_n$C(O)R^8; and ring B is phenyl, pyridyl or a diazine ring). In addition, the document discloses already one specific embodiment within the overlapping range and its preparation according to process (a) of present claim 9 (cf. page 226, step 8). Hence, the present claims 1 and 3-9 lack

novelty in view of **D2**.

2.2 **D3** discloses histamine H_3 receptor antagonists and reverse agonists (page 7, lines 26-35) according to the present formula (I) wherein R^1 is C_{2-6}alkyl or -$(CH_2)_m$-C_{3-7}cycloalkyl and R^2 is -X-heterocyclyl (cf. claim 1; and e.g. examples E2, E12, E18, E29, E30, E48 for specific embodiments within the overlapping range).

D4 shows further H_3 receptor antagonists and reverse agonists (page 14, lines 12-21) of the present formula (I) wherein R^1 is C_{3-7}cycloalkyl and R^2 is as in the present application (cf. claim 1 and the examples e.g. E1, E2, etc.).

D5 relates to a process for the preparation of radiolabelled compounds. In this context the document discloses two compounds of the present formula (I) (cf. page 17, structural formulae).

D6, finally, discloses MAO-B inhibitors of the present formula (I) wherein R^1 is optionally substituted C_{2-3} alkyl and R^2 is -CH_2-(optionally substituted phenyl) (cf. claim 1, R^2 = C_{1-3}alkyl, C(O)R^6; R^6 = -CH_3, -CH_2OCH_3; and e.g. example 1 for a specific embodiment within the overlapping range).

D3 to **D6** are likely to become relevant to the question of novelty of present claims in the regional phase.

3 Inventive Step and Unity of Invention

Insofar as the application relates to novel compounds (I) the following observation would apply to the requirements of inventive step and unity of invention.

3.1 The application describes the preparation of certain compounds (I) and shows that such compounds act as histamine H_3 receptor antagonists (the application, page 36).

3.2 **D1** discloses already compounds (I) of histamine H_3 receptor antagonistic activity wherein R^1 is C_{1-4}alkyl or -CH_2-C_{3-7}cycloalkyl and R^2 is piperidin-1-yl-C_{2-5}alkyl- or pyrrolidin-1-yl-C_{2-5}alkyl-. Starting from **D1** as most relevant state of the art, the problem underlying the application may be seen in the provision of further histamine H_3 receptor antagonists. In view of the very close structural relationship of certain present compounds (I) (e.g. those which differ from those of **D1** in having a R^1 C_{5-6}alkyl or a -$(CH_2)_2$-C_{3-7}cycloalkyl group) and those of **D1**, the present compounds (I)

appear to represent merely obvious alternatives of the compounds of **D1**. Hence, in the absence of any substantiated unexpected effect(s) of the present compounds (I) compared with the respective structurally closest related compounds of **D1**, no inventive activity would be seen in the claimed subject matter.

In addition, the terms "aryl", "heteroaryl", and "heterocyclyl" used in claim 1 are open-ended and thus likely to comprise structures which will not solve any relevant technical problem. Thus, no inventive step would be acknowledged for open-ended compounds (I) and subject-matter referring to them.

Therefore, the present claims 1-9 do at present not meet the requirements of inventive step.

3.3 Furthermore, for the requirement of unity to be met the subject-matter should be characterized by a common distinguishing feature over the compounds of **D1**. Such common distinguishing feature is at present, however, not evident. Consequently, there is a lack of unity in the sense of Rules 13.1 and 13.2 PCT, and the claimed subject-matter may be divided into different groups of inventions as a function of the substituents R^1 and/or R^2.

4 Industrial Applicability

For the assessment of the present claim 7 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*

WO 2004/035544 A1	29.04.2004	14.10.2003	16.10.2002
WO 20047056369 A1	08.07.2004	18.12.2003	20.12.2002
WO 2005/014479 A2	17.02.2005	05.08.2004	08.08.2003

Re Item VIII

Certain observations on the international application

The application does not comply with the requirements of Article 6 PCT for the following reasons.

1 Claim 2 is to be objected under Article 6 in combination with Rule 6.2(a) PCT for referring to the examples in the description.

2 Claim 9 is directed to a process for the preparation of compounds (I) comprising five process steps (a) to (e). However, it is not apparent how compounds (III) defined in process step (b) are accessible from compounds (II) of process step (a) wherein R^1 is different from hydrogen. In addition, process step (d) refers to "compound of formula (I) which is protected". However, none of the current claims gives any indication of the formula of such "protected compound (I)", thereby resulting in a lack of clarity of the claim.